Functional Multiparametric Magnetic Resonance Imaging of the Kidneys Using Blood Oxygen Level-Dependent and Diffusion-Weighted Sequences: a Reliable Tool for Monitoring Acute Upper Urinary Tract Obstruction

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Abstract: PURPOSE: Little data is available on noninvasive MRI-based assessment of renal function during upper urinary tract (UUT) obstruction. In this study, we determined whether functional multiparametric kidney MRI is able to monitor treatment response in acute unilateral UUT obstruction. MATERIAL AND METHODS: Between 01/2008 and 01/2010, 18 patients with acute unilateral UUT obstruction due to calculi were prospectively enrolled to undergo kidney MRI with conventional, blood oxygen level-dependent (BOLD) and diffusion-weighted (DW) sequences on emergency admission and after release of obstruction. Functional imaging parameters of the obstructed and contralateral unobstructed kidneys derived from BOLD (apparent spin relaxation rate [R2*]) and DW (total apparent diffusion coefficient [ADCT], pure diffusion coefficient [ADCD] and perfusion fraction [FP]) sequences were assessed during acute UUT obstruction and after its release. RESULTS: During acute obstruction, R2* and FP values were lower in the cortex (p=0.020 and p=0.031, respectively) and medulla (p=0.012 and p=0.190, respectively) of the obstructed compared to the contralateral unobstructed kidneys. After release of obstruction, R2* and FP values increased both in the cortex (p=0.016 and p=0.004, respectively) and medulla (p=0.071 and p=0.044, respectively) of the formerly obstructed kidneys to values similar to those found in the contralateral kidneys. ADCT and ADCD values did not significantly differ between obstructed and contralateral unobstructed kidneys during or after obstruction. CONCLUSIONS: In our patients with acute unilateral UUT obstruction due to calculi, functional kidney MRI using BOLD and DW sequences allowed for the monitoring of pathophysiologic changes of obstructed kidneys during obstruction and after its release.

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Functional Multiparametric Magnetic Resonance Imaging of the Kidneys Using Blood Oxygen Level-Dependent and Diffusion-Weighted Sequences: a Reliable Tool for Monitoring Acute Upper Urinary Tract Obstruction

Gianluca Giannarini[1], Thomas M. Kessler[2], Beat Roth[1], Peter Vermathen[3], Harriet C. Thoeny[3]

[1]Department of Urology, University of Bern, Inselspital, Bern, Switzerland
[2]Neuro-Urology, Spinal Cord Injury Centre & Research, University of Zurich, Balgrist University Hospital, Zurich, Switzerland
[3]Department of Radiology, Neuroradiology and Nuclear Medicine, Institute of Diagnostic, Interventional and Pediatric Radiology, University of Bern, Inselspital, Bern, Switzerland

Corresponding author:
Prof. Harriet C. Thoeny, M.D.
Department of Radiology, Neuroradiology and Nuclear Medicine
Institute of Diagnostic, Interventional and Pediatric Radiology
University of Bern
Inselspital
Freiburgstrasse 10
CH-3010 Bern, Switzerland
Tel: +41.31.632.2939
Fax: + 41.31.632.4874
E-mail: harriet.thoeny@insel.ch

Running Head: Functional MRI for monitoring upper urinary tract obstruction

Keywords: functional MRI, diffusion weighted MRI; kidney; upper urinary tract; ureteral obstruction; urinary calculi

Abstract

Purpose: Little data is available on noninvasive MRI-based assessment of renal function during upper urinary tract (UUT) obstruction. In this study, we determined whether functional multiparametric kidney MRI is able to monitor treatment response in acute unilateral UUT obstruction**.**

Material and Methods: Between 01/2008 and 01/2010, 18 patients with acute unilateral UUT obstruction due to calculi were prospectively enrolled to undergo kidney MRI with conventional, blood oxygen level-dependent (BOLD) and diffusion-weighted (DW) sequences on emergency admission and after release of obstruction. Functional imaging parameters of the obstructed and contralateral unobstructed kidneys derived from BOLD (apparent spin relaxation rate [R2*]) and DW (total apparent diffusion coefficient [ADC_T], pure diffusion coefficient [ADC_D] and perfusion fraction [F_P]) sequences were assessed during acute UUT obstruction and after its release.

Results: During acute obstruction, R2* and F_P values were lower in the cortex (p=0.020 and p=0.031, respectively) and medulla (p=0.012 and p=0.190, respectively) of the obstructed compared to the contralateral unobstructed kidneys. After release of obstruction, R2* and F_P values increased both in the cortex (p=0.016 and p=0.004, respectively) and medulla (p=0.071 and p=0.044, respectively) of the formerly obstructed kidneys to values similar to those found in the contralateral kidneys. ADC_T and ADC_D values did not significantly differ between obstructed and contralateral unobstructed kidneys during or after obstruction.

Conclusions: In our patients with acute unilateral UUT obstruction due to calculi, functional kidney MRI using BOLD and DW sequences allowed for the monitoring of pathophysiologic changes of obstructed kidneys during obstruction and after its release.

Introduction

UUT obstruction is a major problem in daily clinical practice. Its diagnosis can be challenging and delayed treatment may irreversibly impair renal function. Indeed, UUT dilation is not pathognomonic for obstruction, and a non-dilated UUT does not exclude obstruction.

Renal diuretic scintigraphy[1] and antegrade perfusion pressure-flow test (Whitaker test)[2] are the current gold standards to diagnose and monitor UUT obstruction. However, both methods have relevant drawbacks limiting their value in daily practice. Renal diuretic scintigraphy often fails to correctly identify obstruction, especially in patients with major UUT dilation, bilaterally dilated UUT or a difference in function between kidneys of <20%[1,3]. Furthermore, it is time-consuming, exposes patients to radiation and provides no information on renal morphology. The Whitaker test is invasive and may overestimate obstructive phenomena leading to a false positive diagnosis of obstruction in cases of reduced renal function[2,4]. Alternatively, excretory urography or contrast-enhanced CT may provide some information, but the need for intravenous contrast medium administration, exposure to ionizing radiation and the risk of fornix rupture have limited their use. Finally, Doppler kidney ultrasound with calculation of the arterial resistive index has long been investigated as a noninvasive radiation-free technique to evaluate UUT obstruction. However, due to lack of standardization and with contrasting data published on its accuracy, its ultimate value in routine practice currently remains limited[5].

Thus, there is an urgent need for a noninvasive, fast and widely available technique to detect and quantify the grade of UUT obstruction, to evaluate the function of each kidney separately, and to monitor the findings longitudinally. While conventional MRI has a limited potential for assessing renal function, functional MRI sequences have shown promising

results in detecting pathophysiologic alterations of the renal tissue[6-8], thereby serving as an indicator of renal excretory function during UUT.

Available functional MRI techniques to detect microstructural and pathophysiologic changes of the kidney without the need of contrast medium administration include BOLD and DW imaging. BOLD imaging provides an indirect estimate of oxygen content of the underlying tissue using deoxyhemoglobin as an endogenous contrast agent[9]. DW imaging quantifies the microscopic mobility of water molecules in the extracellular extravascular space, giving simultaneous information on diffusion and perfusion of the underlying tissue, provided that these two entities can be separated[10].

We have recently demonstrated that functional MRI using BOLD and DW sequences allows for noninvasive analysis of functional alterations of the obstructed and unobstructed kidneys during acute unilateral UUT obstruction[11,12].

Thus, the aim of this prospective longitudinal study was: 1) to assess the potential of BOLD and DW sequences to monitor treatment response after acute unilateral UUT obstruction, as exemplified in patients with ureteral calculi, in order to ultimately determine their clinical value in this context; 2) to compare these two techniques within the same patient cohort.

Materials and Methods

Patients

This trial was registered at www.clinicaltrials.gov (NCT00575432). After study approval by the independent ethics committee of the Kanton Bern, all consecutive patients referred to the emergency department of the University Hospital of Bern between January 2008 and January 2010 with acute unilateral flank pain due to urinary calculi were screened. Inclusion criteria were age >18 years, a single unilateral ureteral calculus diagnosed on unenhanced CT and serum creatinine on admission within upper range limit (<110 µmol/l). Exclusion criteria were clinical symptoms/signs of obstructive pyelonephritis, medical history of renal disease, diabetes mellitus and arterial disease, previous kidney and UUT surgery, unavailability of the MRI unit delaying active calculus treatment, and general contraindications to MRI.

Of 265 screened patients, 18 were eventually enrolled in the study after obtaining written informed consent. Some of these patients were part of one of our previous reports[12].

Patients received standardized analgesic treatment consisting of metamizol 1000 mg and diclofenac 75 mg intravenously, and additionally pethidine 25 mg intravenously or 50 to 75 mg subcutaneously as deemed necessary. Excessive hydration was avoided to reduce the risk of fornix rupture, but no standard infusion protocol was established.

MRI of the kidneys with conventional, BOLD and DW sequences to assess changes in renal function during the obstruction phase was invariably performed before any calculus treatment.

Treatment consisted of conservative management, medical expulsive treatment with oral tamsulosin 0.4 mg daily and oral diclofenac 100 mg daily, or extracorporeal shock wave lithotripsy, as appropriate.

MRI of the kidneys with conventional, BOLD and DW sequences to monitor treatment response was repeated within 6 months following calculus passage or lithotripsy, after documentation of a calculus-free status using conventional follow-up examinations (ultrasound and/or X-rays or unenhanced CT).

Magnetic resonance imaging

MRI of the kidneys was performed on a 1.5 T scanner (Sonata, Siemens, Erlangen, Germany) using a combination of an anterior and posterior 6-channel body coil. Technical details on conventional, BOLD and DW sequences have been previously reported[11,12]. Total examination time was 15 to 20 minutes. Data was evaluated on an independent workstation, and post-processing was performed using an in-house-built program based on ImageJ (United States National Institutes of Health, Bethesda, MD, USA) for BOLD sequences and on Interactive Data Language (Research Systems Inc., Boulder, CO, USA) for DW sequences. All images were anonymized and examination date was deleted. Thereafter, image analysis of both kidneys during obstruction and after its release was performed separately for conventional, BOLD and DW sequences by two readers working in consensus and blinded to all clinical data.

Morphological analysis was performed on conventional MRI. Corticomedullary differentiation (normal, reduced, absent), perirenal stranding (absent, moderate, marked), perirenal fluid collection suggestive of fornix rupture (absent, present), UUT dilation (absent, mild, moderate, severe) and concomitant focal renal lesions (absent, present) were noted.

Functional analysis was performed with BOLD and DW sequences as previously described[11,12]. Details are reported in Appendix 1.

Study outcomes and statistical analyses

Primary outcome was validation of functional MRI using BOLD and DW sequences as a tool to monitor acute unilateral UUT obstruction. Thus, changes in functional imaging parameters derived from BOLD (R2*) and DW (ADC_T, ADC_D and F_P) sequences in both obstructed and contralateral unobstructed kidneys were assessed during obstruction and after its release. Secondary outcome was comparison of changes in functional imaging parameters between BOLD and DW sequences.

In the absence of a reference test for diagnosis of UUT obstruction, we assumed that all patients had obstruction to a certain extent because they were all referred to the emergency department with acute flank pain and underwent MRI relatively early after its onset.

Sample size was calculated by a power analysis based on our previous findings during obstruction[11,12]. As for R2*, relatively large differences were obtained between obstructed and unobstructed kidneys, while interquartile ranges were small. According to these conditions, a R2* change after release of only 1.6 s^{-1} could be detected with 18 subjects at a significance level of 0.05 and 80% statistical power, which is much less than the previously detected difference between obstructed and unobstructed kidneys[11]. As for F_P, a change of 3.8% could be detected after release of obstruction with 18 subjects at a significance level of 0.05 and 80% statistical power. This change corresponds to the difference between obstructed and unobstructed kidneys in our previous study[12], i.e. would be compatible with a complete normalization after release. No power calculation was performed for ADC_T and ADC_D values, because they were not significantly different between obstructed and unobstructed kidneys in our previous study[12].

Continuous variables were non-normally distributed according to Kolmogorov-Smirnov test and are reported as median with full and interquartile range. The Wilcoxon test was used to compare the functional imaging parameters (R2*, ADC_T, ADC_D and F_P) of

obstructed and contralateral unobstructed kidneys during acute UUT obstruction and after its release. Pearson correlation analysis was used to correlate the functional imaging parameters of the obstructed kidneys with time between the onset of symptoms and MRI. In addition, R2* values were correlated with F_P values in the obstructed kidneys during acute obstruction. Because our hypotheses were based on our previous findings during obstruction[11,12], no corrections for multiple comparisons were applied. However, as a more conservative approach, all reported p-values were obtained using two-sided instead of one-sided tests with statistical significance set at 0.05. All analyses were performed with PASW Statistics® version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Median age was 43 years (full and interquartile range; 25-66, 15) and median largest calculus size was 4 mm (full and interquartile range: 2-7, 2) (Table 1).

Morphological analysis

During obstruction, corticomedullary differentiation was normal in 13 and reduced in 5 obstructed kidneys. Perirenal stranding was absent in 6, moderate in 5 and marked in 7. Perirenal fluid collection was present in 5. UUT dilation was absent in 6, mild in 5, moderate in 5 and severe in 2. In contralateral unobstructed kidneys, corticomedullary differentiation was normal in 15 and reduced in 3. Perirenal stranding was absent in 10, moderate in 6 and marked in 2. Perirenal fluid collection was absent in all and UUT dilation was present (mild) in 1. Focal lesions (Bosniak I and II cysts, all ≤1 cm in size) were observed in 7 kidneys.

After release of obstruction, in formerly obstructed kidneys corticomedullary differentiation was normal in 15 and reduced in 3. Perirenal stranding was absent in 11, moderate in 6 and marked in 1. Perirenal fluid collection and UUT dilation were absent. In contralateral kidneys, corticomedullary differentiation was normal in 15 and reduced in 3. Perirenal stranding was absent in 10, moderate in 7 and marked in 1. Perirenal fluid collection was absent in all and UUT dilation was present (mild) in 1. All focal lesions were unchanged.

Functional analysis

BOLD sequences

During obstruction, R2* values of obstructed kidneys were lower compared to contralateral unobstructed kidneys both in the cortex and in the medulla (p=0.020 and p=0.012, respectively), indicating increased oxygen content. After release of obstruction, R2*

values of formerly obstructed kidneys increased to values similar to those found in contralateral unobstructed kidneys both in the cortex (p=0.016) and in the medulla (p=0.071) (Table 2, Figure 1).

DW sequences

During obstruction, ADC_T and ADC_D values did not significantly differ between obstructed and contralateral unobstructed kidneys in the cortex and the medulla. However, F_P values of obstructed kidneys were lower in the cortex (p=0.031) and medulla (p=0.190), compared to those of contralateral unobstructed kidneys, indicating reduced cortical microperfusion. After release of obstruction, ADC_T and ADC_D values in the cortex and medulla remained unchanged in both kidneys with no significant difference compared to values during obstruction. F_P values of the formerly obstructed kidneys increased to values similar to those found in the contralateral unobstructed kidneys in the cortex (p=0.004) and medulla (p=0.044) (Table 2, Figure 1).

Correlation analyses

No significant correlation was found between the functional imaging parameters of the obstructed kidneys and time between the onset of symptoms and MRI.

No significant correlation was found between R2* and F_P values either in the cortex or medulla in the obstructed kidneys during obstruction.

Discussion

Our study shows, to our knowledge for the first time, that functional MRI of the kidneys using BOLD and DW sequences may be a reliable tool to noninvasively monitor the treatment of acute unilateral UUT obstruction, as exemplified in patients with ureteral calculi. On the one hand, we confirmed the findings of our previous studies[11,12], since an increased oxygen content noted in BOLD sequences and a decreased microperfusion noted in DW sequences was observed in obstructed compared to contralateral unobstructed kidneys. On the other hand, we observed, as a novel finding, that oxygen content and microperfusion of obstructed kidneys normalized to values of contralateral unobstructed kidneys after successful release of obstruction.

Interestingly, BOLD MRI was more sensitive than DW MRI in this particular context. In fact, only for BOLD sequences significant pathophysiologic changes during acute obstruction were observed in the medulla in addition to the cortex. This is not unexpected, because oxygen content is physiologically lower in the medulla than in the cortex, thus the medulla is more prone to suffer from subtle changes in oxygen content that can be depicted on BOLD MRI[9]. Alternatively, this finding can be explained by the fact that delineation of ROIs is easier for BOLD than for DW images, especially in the medulla, due to their higher spatial resolution.

Concerning DW sequences, although no significant changes were observed for ADC_T and ADC_D values, F_P values in the cortex could still significantly discriminate between obstruction and its release. In fact, as previously shown for the diagnosis of UUT obstruction[12], only the separate assessment of perfusion and diffusion contributions allows for the clinical application of this technique.

Importantly, our patients might have had different grades of UUT obstruction, which were not possible to quantify. However, all patients underwent MRI relatively early after the onset of symptoms, as reflected by the lack of correlation between functional imaging parameters of the obstructed kidneys and time between the onset of symptoms and MRI.

Moreover, no correlation was found between the functional imaging parameters in the obstructed kidneys during obstruction, which we interpret as indirect evidence that both BOLD and DW sequences would be required for a reliable MRI assessment of these cases.

There are several potential clinical applications of functional MRI techniques.

First, functional MRI may be used to monitor expulsion of ureteral calculi during conservative/medical therapy or after lithotripsy. Especially patients with ureteral calculi that are radiolucent to conventional X-rays (e.g. uric acid calculi) or are associated with no or only mild UUT dilation may benefit, thus eliminating the need for multiple CT sessions with increased exposure to ionizing radiation[13].

Second, functional MRI may be used for treatment monitoring of UUT obstruction unrelated to calculi (e.g. pyelo-ureteral junction stenosis, transplanted kidneys, urinary diversion, and pregnancy). In contrast to excretory urography and contrast-enhanced CT, as well as renal diuretic scintigraphy, functional MRI provides simultaneous information on morphology and function of both kidneys in a short time without radiation exposure. Moreover, with functional MRI there is no need for intravenous contrast medium or diuretics administration, which increases the risk of fornix rupture in patients with obstruction. This modality would, thus, be extremely useful in the most challenging scenarios, e.g. patients with renal failure, known allergy to contrast medium, children and pregnancy. Finally, a diagnosis of obstruction would be possible regardless of UUT dilation.

Third, information on changes in renal oxygen content during obstruction could provide insights into early worsening of the function of the individual kidney prior to the

onset of irreversible damage, thus triggering the most appropriate treatment without delay. A further implication concerns the use of non-steroidal anti-inflammatory drugs for pain control during UUT obstruction, which are associated with a relatively high incidence of renal toxicity. High oxygen content in the obstructed kidney as seen with BOLD sequences could indicate marginal functional reserve in the presence of an increased exposure to oxidative stress, which would prompt alternative pathways for analgesia.

Our study is not devoid of limitations. First, there was no reference test for diagnosis of UUT obstruction. As mentioned earlier, however, none of the available methods is 100% accurate in diagnosing obstruction. Second, although significant differences were found for R2* and F_P values between obstructed and unobstructed kidneys, the absence of significant differences in other respects (i.e. correlation analyses) may be due to the relatively limited sample size of our study. Third, despite blinding the readers to clinical data, a potential bias when analyzing the results was unavoidable, since in some patients the obstruction side could be seen on MR images used for ROI selection due to morphological changes (e.g. perirenal fluid collection). Fourth, albeit feasible on all MR units, these functional techniques require training and close cooperation with a dedicated physicist. Moreover, a comparative cost-effectiveness analysis between these MRI-based techniques and the conventional ones is mandatory before their dissemination into clinical practice.

Conclusions

In our relatively small cohort of patients with acute unilateral UUT obstruction due to calculi, functional MRI using BOLD and DW sequences allowed for the monitoring of pathophysiologic changes of obstructed kidneys during obstruction and after its release. Both sequences could significantly discriminate obstruction-related changes; however, BOLD sequences were more sensitive to detect smaller changes, particularly in the medulla.

Thus, multiparametric functional MRI of the kidneys holds potential as a reliable noninvasive tool for monitoring treatment response in patients with UUT obstruction due to various etiologies, with the advantages of neither contrast medium administration nor exposure to ionizing radiation. Validation of this technique in larger scale studies is required.

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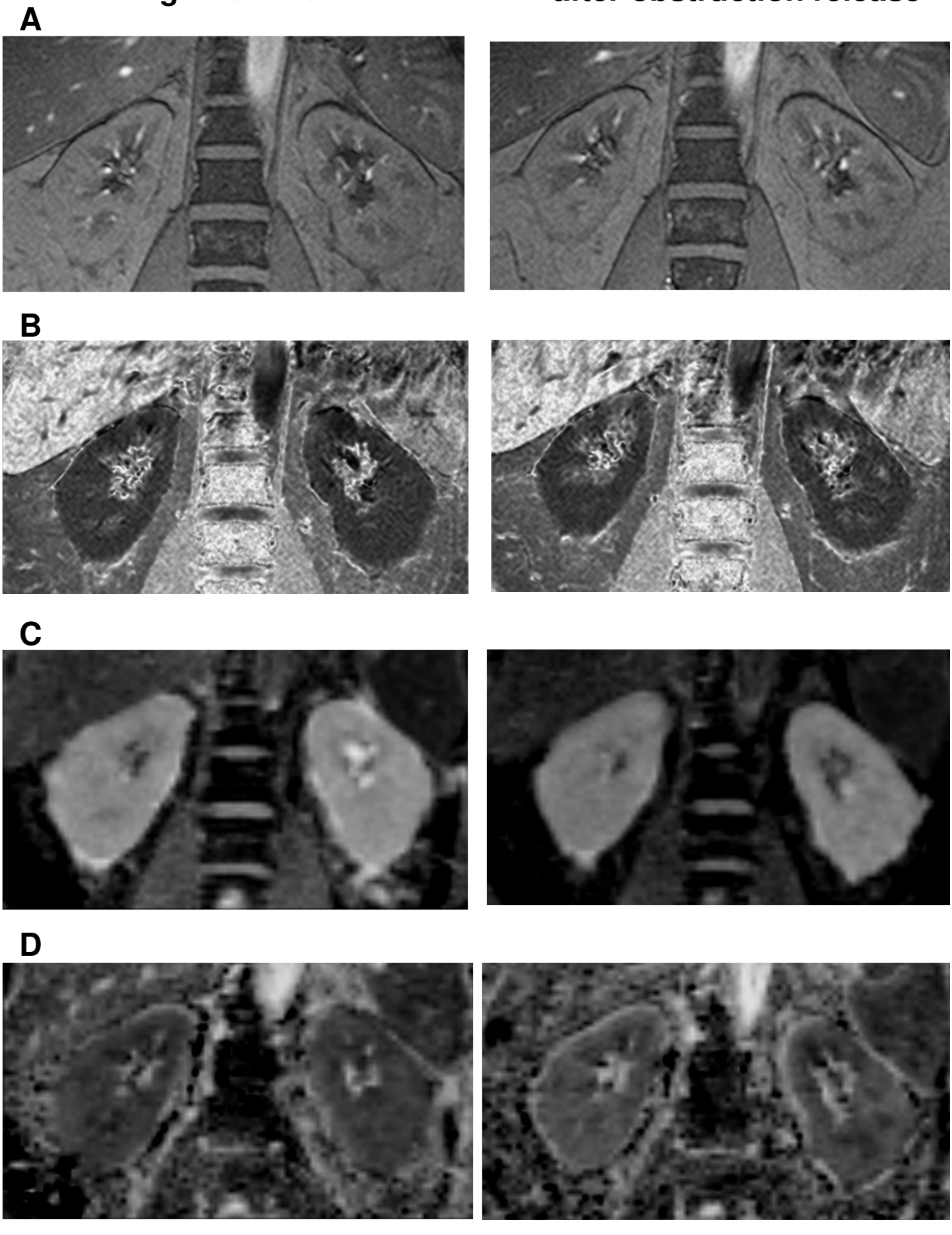
447 **Figure Legends**

448

449 Figure 1. Multiparametric MRI performed during acute obstruction of the left kidney due to a
450 distal ureteral calculus, and three months after successful release of obstruction in a 53-year-
451 old man. Coronal images are shown for the different sequences: A) T1-weighted blood
452 oxygen level-dependent (BOLD) images, acquired with an echo time of 6 ms, and B)
453 corresponding calculated apparent spin relaxation rate (R2*) map images; images for the C)
454 total apparent diffusion coefficient (ADC_T) map, and the D) perfusion fraction (F_P) map.
455 A challenging example of upper urinary tract obstruction is presented with neither upper
456 urinary tract dilatation nor perirenal fluid collection. Furthermore, on morphological analysis
457 no differences between the left obstructed and contralateral unobstructed kidney are evident.
458 It is only with the quantitative analysis that an obstruction of the left kidney can be diagnosed
459 and monitored. In the present case, differences between the obstructed and contralateral
460 unobstructed kidney were: -21% and -35% (in the cortex and medulla, respectively) for R2*,
461 and -29% and -16% (in the cortex and medulla, respectively) for F_P, in the left obstructed
462 kidney. After successful release of obstruction, the corresponding differences were: -3% and
463 +1% (in the cortex and medulla, respectively) for R2*, and +2% and -4% (in the cortex and
464 medulla, respectively) for F_P, in the left, formerly obstructed, kidney.



Appendix 1. Functional MRI analysis.

Apparent spin relaxation rate (R2*) maps were calculated on a pixel-by-pixel basis by fitting the log of the signal intensity versus the echo time to a weighted linear function. Apparent diffusion coefficient (ADC) values were calculated on a pixel-by-pixel basis. First, a single total ADC value (ADC_T) was calculated from all data, despite different contributions from diffusion and perfusion. This method corresponds to the commonly applied procedure. Subsequently, the perfusion fraction (F_P), representing the contribution of microcirculation of blood and movement in predefined structures (such as tubular flow) to the signal decay, and an ADC value mainly reflecting pure diffusion (ADC_D) were calculated. This was possible because the acquisition of multiple b-values as in our study allowed for the separation of diffusion and "microperfusion" contributions to the signal decay.

Circular or ellipsoidal regions of interest (ROIs) were delineated on blood oxygen level-dependent (BOLD) images with an echo time of 6 ms, and on diffusion-weighted images acquired at a b-value of 0 s/mm^2, respectively, and placed in the upper pole, mid-level and lower pole of the cortex and medulla on a single section for each kidney separately. Subsequently, as for BOLD images, the ROIs were copied to the various echo times and fitted to the respective signal intensities to generate R2* maps. As for diffusion-weighted images, the ROIs were copied to the various b-value images and diffusion maps including ADC_T, ADC_D and F_P were calculated.

Abbreviations and Acronyms

ADC_D	=	pure apparent diffusion coefficient
ADC_T	=	total apparent diffusion coefficient
BOLD	=	blood oxygen level-dependent
CT	=	computed tomography
DW	=	diffusion weighted
F_P	=	perfusion fraction
MR	=	magnetic resonance
MRI	=	magnetic resonance imaging
R2*	=	apparent spin relaxation rate
ROI	=	region of interest
UUT	=	upper urinary tract